Remarks/Arguments

Reconsideration of the application in view of the above amendments and following remarks is requested. Claims 25, 27, 28, 30, 31, and 33 are now in the case. Claims 25, 27, 28, and 31 have been amended. Claim 33 has been added. Claims 26, 29, and 32 have been canceled. No new matter has been added.

Entry of the above amendments is requested. These amendments have been made solely to advance the prosecution of certain subject matter and are believed to obviate the Office's rejections of the claims. In the event that rejection of the claims is maintained, the amendments are believed to present the claims in better form for consideration on appeal. Applicants do not acquiesce in the merits of any rejection and reserve the right to prosecute claims to canceled subject matter in one or more continuing applications.

The Office rejected claims 25-28 and 30-31 under 35 U.S.C. 112, first paragraph, on the grounds that the specification does not reasonably provide enablement for treatment of all types of kidney fibrosis or glomerulonephritis with antibodies as broadly claimed. The Office believes that the specification is enabling for administering humanized or human monoclonal antibodies that bind to an epitope of a protein as shown in SEQ ID NO:2 from amino acid residues 258-370 for the treatment of mesangial proliferative glomerulonephritis, diabetic nephropathy or lupus nephritis.

This rejection is traversed in part and overcome in part.

Claim 25 has been amended to recite that the antibody is a humanized monoclonal antibody or a human monoclonal antibody. The remaining claims include this limitation by virtue of their dependence on claim 25. Support for this amendment is found within the application as filed, such as at page 17, lines 4-13.

Claim 25 has also been amended to recite that the fibroproliferative disorder is characterized by mesangial cell proliferation. The remaining claims include this limitation by virtue of their dependence on claim 25. Support for this amendment is found throughout applicants' specification, such as at page 1, lines 27-28; page 3, line 30 to page 4, line 3; page 6, lines 31-32; page 13, lines 3-8; and pages 37-38. The Office has acknowledged that applicants "have effectively demonstrated a nexus between mesangioproliferative renal disease and zvegf4 overexpression and amelioration with monoclonal antibodies to zvegf4."

Claims 28 and 31 have been amended to remove the recitation of glomerulonephritis. These claims have also been amended to recite membranoproliferative glomerulonephritis, diffuse proliferative glomerulonephritis, diabetic nephropathy, and lupus nephritis. Support for this amendment is found within applicants' specification, for example at

page 14, lines 26-31. These conditions are characterized by mesangial cell proliferation and extracellular matrix accumulation. With regard to the newly recited membranoproliferative glomerulonephritis and diffuse proliferative glomerulonephritis, applicants submit herewith two references disclosing the involvement of mesangial cell proliferation (Stedman's Medical Dictionary, 26th ed., 726-727, 1995; Salifu et al., eMedicine, Topic 882, 2006; copies enclosed).

The Office has characterized applicants' specification as being "enabling for administering humanized or human monoclonal antibodies that bind to an epitope of a protein as shown in SEQ ID NO:2 from amino acid residues 258-370" (Office Action at page 2) and has characterized claims 25, 28, 30, and 31 as reciting "treatment with an antibody to an epitope of a protein as shown in SEQ ID NO:2 from amino acid residues 258-370" (Office Action at page 3). However, claims 25 and 28 are directed to antibodies that specifically bind to an epitope of a protein as shown in SEQ ID NO:2 from amino acid residue 19 to amino acid residue 370. Support for this recitation is found throughout applicants' specification, such as at page 9; page 17, line 34 – page 18, line 7; and pages 32-33 (wherein the immunogenic peptide huzvegf4-1 (SEQ ID NO:9) comprises residues 131-148 of SEQ ID NO:2 and peptide huzvegf4-2 (SEQ ID NO:10) comprises residues 230-253 of SEQ ID NO:2). Applicants respectfully submit that the full scope of the amended claims is enabled.

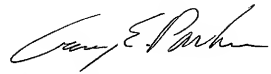
The rejection of claims 29 and 32 has been obviated by the cancellation of these claims.

New claim 33 recites that the fibroproliferative disorder is further characterized by extracellular matrix accumulation. Support for this amendment is found throughout applicants' specification, such as at page 1, lines 27-28; page 3, line 30 to page 4, line 5; and page 6, lines 31-32. Applicants submit that a nexus between zvegf4 overexpression and extracellular matrix production has been established. Confirmation of such a nexus was provided in the Declaration of Debra G. Gilbertson Under 37 C.F.R. § 1.132 dated March 30, 2006.

Applicants believe that each rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6673.

It is believed that no fee is due. However, in the event that a fee is due, please charge any fee or credit any overpayment to Deposit Account No. 26-0290.

Respectfully Submitted,



Gary E. Parker
Registration No. 31,648

Enclosures:
Stedman's Medical Dictionary, 26th ed., 726-727, 1995
Salifu et al., eMedicine, Topic 882, 2006

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STEDMAN'S Medical Dictionary

26th Edition

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from pooled liquid human plasma from a number of donors and may be prepared by precipitation with organic solvents under controlled conditions of pH, ionic strength, and temperature. SYN human normal immunoglobulin.

immune serum g., a sterile solution of g.'s that contains many antibodies normally present in adult human blood; a passive immunizing agent frequently used for prophylaxis against hepatitis A.

measles immune g. (human), a sterile solution of g.'s derived from the blood plasma of normal adult human donors; it is prepared from immune serum g. that complies with the measles antibody reference standard; a passive immunizing agent. SYN measles immunoglobulin.

pertussis immune g., a sterile solution of g.'s derived from the plasma of adult human donors who have been immunized with pertussis vaccine; used both prophylactically and therapeutically. SYN pertussis immunoglobulin.

plasma accelerator g., SYN *factor* V.

poliomyelitis immune g. (human), a sterile solution of g.'s that contains those antibodies normally present in adult human blood; it is a passive immunologic agent that attenuates or prevents poliomyelitis, measles, and infectious hepatitis, and confers temporary but significant protection against paralytic polio. SYN poliomyelitis immunoglobulin.

rabies immune g. (human), g. fraction of pooled plasma of high anti-rabies virus titer from immunized persons. SYN rabies immunoglobulin.

RH_0(D) immune g., a g. fraction of antibody, derived from human donors, specific for the most common antigen, Rh_0(D), of the Rh group; used to prevent Rh-sensitization of an Rh-negative woman after delivery of an Rh-positive fetus. SYN anti-D immunoglobulin, Rh_0(D) immunoglobulin.

serum accelerator g., a substance in serum that accelerates the conversion of prothrombin to thrombin in the presence of thromboplastin and calcium; produced by the action of traces of thrombin upon plasma accelerator g.

sex hormone-binding g. (SHBG), a plasma β-g., produced by the liver, that binds testosterone and, with a weaker affinity, estrogen; serum levels of SHBG in women are twice the levels seen in men; serum concentrations are increased in certain types of liver disease and in hyperthyroidism; are decreased with advancing age, by androgens, and in hypothyroidism. SYN testosterone-estrogen-binding g.

sex steroid-binding g., SYN gonadal steroid-binding g.

specific immune g. (human), g. fraction of pooled serums (or plasma) selected for high titer of antibodies specific for a particular antigen, or from persons specifically immunized.

testosterone-estrogen-binding g., SYN sex hormone-binding g.

tetanus immune g., a sterile solution of g.'s derived from the blood plasma of adult human donors who have been immunized with tetanus toxoid; a passive immunizing agent. SYN tetanus immunoglobulin.

thyroxine-binding g. (TBG), an α-globulin of blood with a strong binding affinity for thyroxine; triiodothyronine is bound to it much less firmly; a deficiency or excess of this protein may occur as a rare benign X-linked disorder. SYN thyroxine-binding protein (1).

zoster immune g., a g. fraction of pooled plasma from individuals who have recovered from herpes zoster; used prophylactically and therapeutically for varicella.

glob·u·li·nu·ria (glob'yū-li-nū'rē-ă). The excretion of globulin in the urine, usually, if not always, in association with serum albumin.

glob·u·lus (glob'yū-lŭs). SYN globule. [L.]

glo·bus, pl. **glo·bi** (glō'bŭs, -bī). **1** [NA]. A round body; ball. 2. SEE globi. SYN globe. [L.]

g. hyster'icus, difficulty in swallowing; a sensation as of a ball in the throat or as if the throat were compressed; a symptom of conversion *disorder*.

g. ma'jor, SYN *head* of epididymis.

g. mi'nor, SYN *tail* of epididymis.

g. pal'lidus [NA], the inner and lighter gray portion of the lentiform nucleus. SEE ALSO paleostriatum. SYN pale globe, pallidum.

glo·mal (glō'măl). Relating to or involving a glomus.

glo·man·gi·o·ma (glō-man-jē-ō'mă). A variant of glomus *tumor*, characterized by multiple tumors resembling cavernous hemangioma.

glo·man·gi·o·sis (glō-man-jē-ō'sis). The occurrence of multiple complexes of small vascular channels, each resembling a glomus.

pulmonary g., g. occurring within small pulmonary arteries in severe pulmonary hypertension and congenital heart disease.

glome (glōm). SYN glomus.

glo·mec·to·my (glō-mek'tō-mē). Excision of a glomus tumor. [L. *glomus* + G. *ektomē*, cutting out]

glom·era (glom'er-ă). Plural of glomus.

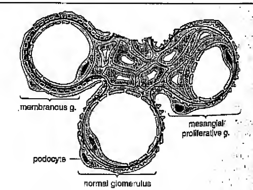
glom·era aor·ti·ca. SYN para-aortic *bodies*, under *body*.

glo·mer·u·lar (glō-mār'yū-lăr). Relating to or affecting a glomerulus or the glomeruli. SYN glomerulose.

glom·er·ule (glom'er-yūl). SYN glomerulus.

glo·mer·u·li·tis (glō-mār'yū-lī'tis). Inflammation of a glomerulus, specifically of the renal glomeruli, as in glomerulonephritis.

glo·mer·u·lo·ne·phri·tis (glō-mār'yū-lō-nef-rī'tis). Renal disease characterized by bilateral inflammatory changes in glomeruli which are not the result of infection of the kidneys. SYN glomerular nephritis. [glomerulus + G. *nephros*, kidney, + -itis, inflammation]



glomerulonephritis (schematic view of two typical forms) left: membranous g., with spikes of basement membrane material, deposits of immunoglobulins, and loss of foot processes; right: mesangial proliferative g., with increase in mesangial cells and matrix, and narrowing of the capillary lumina

acute g., g. that frequently occurs as a late complication of pharyngitis, especially due to type 12 β-hemolytic streptococci, characterized by abrupt onset of hematuria, edema of the face, oliguria, and variable azotemia and hypertension; the renal glomeruli usually show cellular proliferation or infiltration by polymorphonuclear leukocytes. SYN acute hemorrhagic g., acute nephritis, acute post-streptococcal g.

acute crescentic g., SYN rapidly progressive g.

acute hemorrhagic g., SYN acute g.

acute post-streptococcal g., SYN acute g.

anti-basement membrane g., g. resulting from anti-basement membrane antibodies, characterized by smooth linear deposits of IgG and C3 along glomerular capillary walls; includes rapidly progressive g. and g. in Goodpasture's syndrome.

Berger's focal g., SYN focal g.

chronic g., g. that presents with persisting proteinuria, chronic renal failure, and hypertension, of insidious onset or as a late sequel of acute g.; the kidneys are symmetrically contracted and granular, with scarring and loss of glomeruli and the presence of tubular atrophy and interstitial fibrosis. SYN chronic nephritis

diffuse g., g. affecting most of the renal glomeruli; it may lead to uremia.

Ellis type 1 g., obsolete designation for g. presenting as acute g., followed by complete recovery in most cases, or the development of rapidly progressive g., or incomplete remission with persistent proteinuria and subsequent development of chronic g. SYN Ellis type 1 nephritis.

Ellis type 2 g., obsolete designation for g. which is usually not related to preceding bacterial infection; characterized by an insidious onset of the nephrotic syndrome, failure of complete remission, and eventual development of chronic renal failure. The kidneys usually show membranous g. SYN Ellis type 2 nephritis.

exudative g., g. with infiltration of glomeruli by polymorphonuclear leukocytes, occurring in acute g.

focal g., g. affecting a small proportion of renal glomeruli which commonly presents with hematuria and may be associated with acute upper respiratory infection in young males, not usually due to streptococci; associated with IgA deposits in the glomerular mesangium and may also be associated with systemic disease, as in Henoch-Schönlein purpura. SYN Berger's disease, Berger's renal g., focal nephritis, IgA nephropathy.

focal embolic g., g. associated with subacute bacterial endocarditis, frequently producing microscopic hematuria without azotemia.

hypocomplementemic g., SYN membranoproliferative g.

immune complex g., immune complexes are deposited in the renal glomerulus where they bind complement and initiate an inflammatory process attracting neutrophils and macrophages resulting in an alteration of the basement layer of the kidney. The disease state can lead to ultimate destruction of the glomerulus and renal failure.

lobular g., SYN membranoproliferative g.

local g., SYN segmental g.

membranoproliferative g., chronic g. characterized by mesangial cell proliferation, increased lobular separation of glomeruli, thickening of glomerular capillary walls and increased mesangial matrix, and low serum levels of complement; occurs mainly in older children, with a variably slow progressive course, episodes of hematuria or edema, and hypertension. It is classified into three types: type 1, the commonest, in which there are subendothelial electron-dense deposits; type 2, dense-deposit disease, in which the lamina densa is greatly thickened by extremely electron-dense material; type 3, in which there are both subendothelial and subepithelial deposits. SYN hypocomplementemic g., lobular g., mesangiocapillary g.

membranous g., g. characterized by diffuse thickening of glomerular capillary basement membranes, due in part to subepithelial deposits of immunoglobulins separated by spikes of basement membrane material, and clinically by an insidious onset of nephrotic syndrome and failure of disappearance of proteinuria; the disease is most commonly idiopathic but may be secondary to malignant tumors, drugs, infections, or systemic lupus erythematosus.

mesangial proliferative g., g. characterized clinically by the nephrotic syndrome and histologically by diffuse glomerular increases in endocapillary and mesangial cells and in mesangial matrix; in some cases, there are mesangial deposits of IgM and complement. SYN diffuse mesangial proliferation, IgM nephropathy.

mesangiocapillary g., SYN membranoproliferative g.

proliferative g., g. with hypercellularity of glomeruli due to proliferation of endothelial or mesangial cells, occurring in acute and membranoproliferative g.

rapidly progressive g., g. usually presenting insidiously, with preceding streptococcal infection, with increasing renal failure leading to death within a few months; at autopsy the kidneys are normal in size, numerous glomerular capsular epithelial crescents are present, and antiglomerular basement membrane antibodies are frequently found. SYN acute crescentic g.

segmental g., g. affecting only part of a glomerulus or glomeruli.

subacute g., undesirable term for g. with proteinuria, hematuria and azotemia persisting for many weeks; renal changes are variable, including those of rapidly progressive and membranoproliferative g. SYN subacute nephritis.

glo-mer-u-lop-a-thy (glō-mĕr-yū-lop'ă-thē). Glomerular disease of any type. [glomerulus + G. *pathos*, suffering]

focal sclerosing g., focal, segmental glomerulosclerosis reported in adults and children with normal serum complement, progressing to chronic glomerulonephritis.

glo-mer-u-lo-scle-ro-sis (glo-mĕr'yū-lō-sklē-rō'sis). Hyaline deposits or scarring within the renal glomeruli, a degenerative process occurring in association with renal arteriosclerosis or diabetes. SYN glomerular sclerosis. [glomerulus + G. *sklērōsis*, hardness]

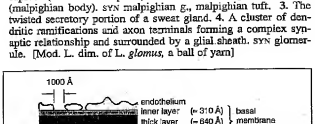
diabetic g., rounded hyaline or laminated nodules in the periphery of the glomeruli with capillary basement membrane thickening and increased mesangial matrix occurring in long-standing diabetes, proteinuria, and ultimately renal failure. SYN intercapillary g.

focal segmental g., segmental collapse of glomerular capillaries with thickened basement membranes and increased mesangial matrix; seen in some glomeruli of patients with nephrotic syndrome or mesangial proliferative glomerulonephritis.

intercapillary g., SYN diabetic g.

glo-mer-u-lose (glō-mĕr'yū-lōs). SYN glomerular.

glo-mer-u-lus, pl. **glo-mer-u-li** (glō-mĕr'yū-lŭs, -yū-lī) [NA]. 1. A plexus of capillaries. 2. A tuft formed of capillary loops at the beginning of each nephric tubule in the kidney; this tuft with its capsule (Bowman's capsule) constitutes the corpusculum renis (malpighian body). SYN malpighian g., malpighian tuft. 3. The twisted secretory portion of a sweat gland. 4. A cluster of dendritic ramifications and axon terminals forming a complex synaptic relationship and surrounded by a glial sheath. SYN glomerule. [Mod. L. dim. of L. *glomus*, a ball of yarn]



glomerulus (schematic cross-section of capillary wall)

juxtamedullary g., a g. close to the medullary border.

malpighian g., SYN glomerulus (2).

g. of mesonephros, one of the tufts of capillary vessels within the mesonephros derived from a lateral branch of the primary aorta; each g. is connected to a tubule.

olfactory g., one of the small spherical territories in the olfactory bulb in which dendrites of mitral and tufted cells synapse with axons of olfactory receptor cells.

g. of pronephros, one of the tufts of capillary vessels in the pronephros derived from a lateral branch of the aorta.

glo-mus, pl. **glom-era** (glō'mŭs, glom'er-ă). 1 [NA]. A small globular body. 2. A highly organized arteriolovenular anastomosis forming a tiny nodular focus in the nailbed, pads of the fingers and toes, ears, hands, and feet and many other organs of the body. The efferent arteriole enters the connective tissue capsule of the g., becomes devoid of an internal elastic membrane, and develops a relatively thick epithelioid muscular wall and small lumen; the anastomosis may be branched and convoluted, richly innervated with sympathetic and myelinated nerves, and connected with a short, thin-walled vein that drains into a periglomic vein and then into one of the veins of the skin. The g. functions as a shunt- or bypass-regulating mechanism in the flow of blood, temperature, and conservation of heat in the part as well as in the indirect control of the blood pressure and other functions of the circulatory system. SYN glandulae glomiformes (1) [NA], glomiform glands, glomus body. SYN glome. [L. *glomus*, a ball]

Glomerulonephritis, Diffuse Proliferative

Last Updated: August 23, 2006

Synonyms and related keywords: lupus nephritis class IV, DPGN, autoimmune disorders, systemic lupus erythematosus, SLE, vasculitis syndromes, Wegener granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, essential mixed cryoglobulinemia, membranoproliferative glomerulonephritis, Henoch-Schönlein purpura, connective tissue diseases, rapidly progressive glomerulonephritis, RPGN, anti–glomerular basement membrane disease, anti-GBM disease, antineutrophil cytoplasmic antibody–associated glomerulonephritis, ANCA-associated glomerulonephritis, crescentic glomerulonephritis, Goodpasture syndrome, microscopic polyarteritis nodosa, PAN

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Disclosure

Associated Infection

Glomerulor Poststreptc

Glomerulor Rapidly Prc

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Patient E

Kidneys a Urinary S Center

Blood in U Overview

Causes o Urine

Blood in U Symptom

Blood in U Treatmen

INTRODUCTION

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Background: Diffuse proliferative glomerulonephritis (DPGN) is a term used to describe a distinct histologic form of glomerulonephritis common to various types of systemic inflammatory diseases, including autoimmune disorders (eg, systemic lupus erythematosus [SLE]), vasculitis syndromes (eg, Wegener granulomatosis), and infectious processes. More than 50% of the glomeruli (diffuse) demonstrate increased mesangial, epithelial, endothelial (proliferative), and inflammatory cells (ie, glomerulonephritis). In contrast, when fewer than 50% of the glomeruli are involved, the condition is termed focal proliferative, an entity with a potential to progress to DPGN. The diagnosis is often suspected in a patient presenting with systemic inflammatory disease who manifests hematuria, proteinuria, and active urinary sediment or azotemia (ie, rise in serum blood urea nitrogen, creatinine); histologic findings from kidney biopsy tissue are used to confirm the diagnosis.

Sporadic forms of renal diseases manifesting as focal, segmental, necrotizing, and crescentic glomerulonephritis or DPGN with undetermined incidence include microscopic polyangiitis; Churg-Strauss syndrome; essential mixed cryoglobulinemia, which also may manifest as membranoproliferative glomerulonephritis; Henoch-Schönlein purpura; and connective tissue diseases.

In severe forms, epithelial proliferation obliterates the Bowman space (ie, crescents). The resulting acute renal failure may manifest as an acute anuria or a steady decline in renal function. Spontaneous remission is rare, and treatment results are anecdotal.

Pathophysiology: Most cases of DPGN result from the deposition of immune complexes in the mesangium,

glomerular basement membrane (GBM), subendothelial or subepithelial locations. Antibodies may form immune complexes with circulating DNA before deposition (ie, immune complex deposition) or may bind directly to nonglomerular antigens already planted in the mesangium or GBM (ie, in situ immune complex formation). In anti-GBM disease, the antibodies act against the GBM. The pathogenesis of antineutrophil cytoplasmic antibody (ANCA)–associated glomerulonephritis is unknown, although microvasculitis is the predominant feature without immune complex formation.

Activation of the complement system through the classic pathway by immune complexes or direct cell-mediated injury in ANCA-associated glomerulonephritis results in the recruitment of inflammatory cellular infiltrates (eg, lymphocytes, macrophages, neutrophils), proliferation of the mesangial and endothelial cells, and necrosis. Cellular crescents and fibrin thrombi may be present in more severe cases. The net result is obliteration of the capillary loops and sclerosis, predisposing the patient to hypertension and renal failure.

The cellular and immunologic attack of the glomerulus renders the GBM permeable to protein, red blood cells, and white blood cells. Therefore, urinalysis during active inflammation characteristically shows an active urinary sediment, ie, red blood cells or casts, white blood cells or casts, and variable degrees of proteinuria (ie, nephritic pattern).

Anti-GBM disease is an autoimmune disease in which autoantibodies are directed against type IV collagen in the GBM. Binding of these autoantibodies to the GBM induces rapidly progressive glomerulonephritis (RPGN) and crescentic glomerulonephritis. The clinical complex of anti-GBM nephritis and lung hemorrhage is Goodpasture syndrome. The typical morphologic pattern using light microscopy is DPGN, with focal necrotizing lesions and crescents in more than 50% of glomeruli (ie, crescentic glomerulonephritis). Acute nephrotic syndrome is rare, and a bimodal peak in incidence exists. Although any age group may be affected, the first peak in incidence occurs in the third to the sixth decades of life and the second occurs in the sixth to the seventh decades of life.

In patients with Wegener granulomatosis, renal biopsy findings typically reveal focal, segmental, necrotizing, pauci-immune glomerulonephritis with crescent formation.

In microscopic polyarteritis nodosa (PAN), the usual histopathologic lesion is a pauci-immune focal segmental necrotizing and crescentic glomerulonephritis. In Churg-Strauss syndrome, a minority of patients may develop focal segmental necrotizing glomerulonephritis; in mixed cryoglobulinemias, the characteristic morphologic lesions are diffuse mesangial proliferative or membranoproliferative glomerulonephritis. For Henoch-Schönlein purpura, light microscopic appearances can vary from mild mesangial proliferation and expansion to diffuse proliferation with glomerular crescents.

In rheumatoid arthritis (RA), lesions of mesangial proliferative glomerulonephritis and basement membrane thickening caused by subepithelial immune deposits may be observed. Occasional cases of focal mesangial proliferative glomerulonephritis with mesangial deposition of immunoglobulin G (IgG) and complement have been described in polymyositis and dermatomyositis.

In addition to poststreptococcal glomerulonephritis, the nephritic syndrome and RPGN can complicate acute immune-complex glomerulonephritis due to other viral, bacterial, fungal, and parasitic infections. Some of these warrant specific mention. Diffuse proliferative immune complex glomerulonephritis is a well-described complication of acute and subacute bacterial endocarditis and usually is associated with hypocomplementemia. The glomerular lesion typically resolves following eradication of the cardiac infection. Shunt nephritis is a syndrome characterized by immune complex glomerulonephritis secondary to infection of ventriculoatrial shunts inserted for treatment of childhood hydrocephalus.

The most common offending organism is coagulase-negative *Staphylococcus*. Renal impairment usually is mild and is associated with hypocomplementemia. Nephrotic syndrome complicates 30% of cases. Acute proliferative glomerulonephritis can also complicate chronic suppurative infections and visceral abscesses. Patients typically present with a fever of unknown origin and an active urine sediment. Although renal biopsy is used to detect immune deposits containing IgG and C3, serum complement levels usually are within the reference range.

Frequency:

- **In the US:** The incidence of SLE in urban areas varies from 15-50 cases per 100,000 population per year. Renal involvement is evident clinically in 40-85% of patients with SLE. DPGN is the lesion observed in 35-40% of biopsies in lupus nephritis, and as many as 30% of these patients progress to terminal renal failure.

  Anti-GBM disease is a rare disorder of unknown etiology with an annual incidence of 0.5 cases per million. About 50-70% of patients have lung hemorrhage; anti-GBM antibodies develop in the serum of more than 90% of patients with anti-GBM nephritis according to findings on specific radioimmunoassay.

  Renal injury occurs in 80% of patients with Wegener granulomatosis. Renal biopsy tissue typically reveals focal, segmental, necrotizing, pauci-immune glomerulonephritis with crescent formation, which may progress to DPGN.

  Cytoplasmic ANCAs are detected at presentation in 80% of patients with renal disease and in 10% more during follow-up. In contrast to the lung, granulomas rarely develop in the kidney.

Most cases of acute poststreptococcal glomerulonephritis are sporadic, although the disease can occur as an epidemic. The characteristic lesion visible using light microscopy is DPGN. Crescents may be present, and extraglomerular involvement usually is mild.

Nephritis is present in 80% of cases of Henoch-Schönlein purpura and manifests as a nephrotic urine sediment and moderate proteinuria. Macroscopic hematuria and nephrotic range proteinuria are uncommon.

- **Internationally:** The incidence of DPGN in renal biopsies varies from approximately 10-27% in Europe and 30% in the Middle East to 41% in Japan. Worldwide, the most common glomerulopathy is due to immunoglobulin A (IgA) nephropathy, accounting in most series for 10-40% of all glomerulonephritis. Up to 80% of patients with Henoch-Schönlein purpura (ie, anaphylactoid purpura), which is a distinct systemic vasculitis syndrome that is characterized by palpable purpura (most commonly distributed over the buttocks and lower extremities), arthralgias, and gastrointestinal signs and symptoms, have DPGN.

  In 1987, after the introduction of assays for antineutrophil cytoplasmic antibodies (ANCA), the diagnosis of ANCA-positive vasculitis (ie, Wegener granulomatosis, microscopic polyarteritis) rose from 1.5 cases per million to about 6-7 cases per million.

Mortality/Morbidity: Advances in immunosuppressive therapy and renal replacement therapy have markedly reduced the mortality and morbidity rates of DPGN in the last 2 decades. A significant portion of morbidity and mortality rates in DPGN is due to complications of immunosuppressive therapy, including drug toxicity and infection.

- In one short-term study consisting of 25 patients with severe lupus whose cases were followed for 9.4 months, the combined crude mortality (1 patient) plus end-stage renal disease ([ESRD] 1 patient) rate was 8%.

- In one 10-year follow-up study of 86 patients treated aggressively (ie, with high-dose prednisone plus oral cyclophosphamide alone or with plasmapheresis) for severe lupus nephritis, patient survival at 5 and 10 years was 95% in the group that had remission. In the group without remission, patient survival was 69% at 5 years and 60% at 10 years. Renal survival rates were 94% at 5 and 10 years in the remission group but 46% at 5 years and 31% at 10 years in the group with no remission.

- Mortality due to poststreptococcal glomerulonephritis is rare. Prior to the introduction of immunosuppressive therapy, more than 80% of patients with anti-GBM nephritis developed ESRD within 1 year, and many patients died from pulmonary hemorrhage or complications of uremia and infection. Renal failure is a poor prognostic marker for survival in patients with Wegener granulomatosis. In a series of 104 patients who presented to the Cleveland Clinic Foundation from 1982-1997, 11 of 23 patients who required dialysis died. In a Norwegian

study of 108 patients with Wegener granulomatosis and renal involvement, 2- and 5-year renal survival rates were 86% and 75%, respectively. The 2- and 5-year patient survival rates were 88% and 74%, respectively. IgA nephropathy has an indolent course with a favorable outcome.

- The actuarial renal survival rate in adults after 10 years is 80-85% in most of the European and Asian studies, is slightly less in studies from the United States, and is more than 90% in the few studies of children. Renal death due to DPGN in IgA nephropathy is rare.

Race: Lupus nephritis has a 3-4 times greater incidence in black patients than in white patients. IgA nephropathy is more common in people of Asian origin than it is in whites of African American origin. Wegener granulomatosis is extremely rare in blacks compared to whites

Sex:

- Men tend to have more aggressive disease than women. However, for SLE, the female-to-male incidence ratio is 9:1 for women of childbearing age. By comparison, the female-to-male ratio is only 2:1 for disease developing during childhood or in people aged 65 or older. Males who develop SLE have the same incidence of renal disease as do females.

- Microscopic PAN is more common in males (ie, male-to-female ratio of 2:1). The distribution of Wegener granulomatosis among the sexes is roughly equal, with a slight male predominance. Males have a 2.7 times higher incidence of IgA nephropathy than females.

Age:

- Patients with Goodpasture syndrome typically are young males aged 5-40 years (the male-to-female ratio is 6:1). In contrast, patients presenting during the second peak in incidence, occurring in the sixth decade of life, rarely experience lung hemorrhage and have an almost equal sex distribution.

- SLE occurs in all age groups, with the peak incidence occurring in women of childbearing age. Over 85% of patients are younger than 55 years.

- Wegener granulomatosis develops in people of any age. Approximately 15% of patients are younger than 19 years, and only rarely does the disease occur before adolescence. The mean age of onset is approximately 40 years. The mean age of patients at onset in reports of PAN and microscopic polyangiitis is 48 years.

History: Focus the history on the causes of DPGN and the associated symptoms. While a minority of patients may be asymptomatic (ie, <15%) and are diagnosed during routine laboratory examination, most patients manifest signs of the primary disease as well as those relating to renal injury.

- Suspect DPGN in patients with SLE, infectious disease processes, a recent streptococcal throat infection, or in patients with sinopulmonary disease who have recent onset of the following:
  - Hypertension
  - Microscopic or gross hematuria
  - Nonnephrotic or nephrotic range proteinuria or an increase in proteinuria from baseline
  - Serum creatinine of more than 0.4 mg/dL from the reference range or the baseline
  - Oligoanuria and symptoms of uremia in severe cases of RPGN with crescent formation
- Also suspect DPGN in a patient with other systemic diseases who has recent onset of the same findings listed above.
- Nonspecific symptoms, including nausea, vomiting, fatigue, or weight loss may indicate uremia or symptoms of the primary disease process.
- A history of rash; photosensitivity; oral ulcers; arthralgias; arthritis; serositis; or a renal, neurologic, hematologic, or immunologic disorder suggests SLE as the primary disease.
- A history of cough, dyspnea, hemoptysis, and renal disease suggests Goodpasture syndrome, but other pulmonary-renal syndromes must be ruled out, including SLE pneumonitis, Wegener granulomatosis, cryoglobulinemia, renal vein thrombosis with pulmonary embolism, legionella infection, and congestive heart

failure.

- Patients with Wegener granulomatosis present with sinopulmonary disease (ie, paranasal sinus pain and drainage with purulent or bloody nasal discharge and occasional nasal mucosal ulceration/perforation, leading to saddle nose deformity), serous otitis media (ie, blockage of the eustachian tube), cough, dyspnea, and hemoptysis.

- Patients with IgA nephropathy (ie, Berger disease) may present with the classic findings of flank pain and gross hematuria following upper respiratory infections. Others may simply have indolent microhematuria found incidentally. Much less commonly, patients present with acute glomerulonephritis, renal failure, and nephrotic syndrome.

Physical:

- If azotemia is present, exclude prerenal and postrenal causes (see Azotemia).

- Nonspecific findings that suggest DPGN

  - Hypertension

  - Fever, present in both infectious and noninfectious glomerulonephritis

- Findings pertaining to SLE include the often acute onset of conjunctivitis, episcleritis, photosensitivity, oral ulcers, malar rash (eg, erythema of the nose and malar eminences in a butterfly distribution), discoid lupus, pleural or pericardial friction rub, psychosis, seizures, nonerosive arthritis, or arthralgia

- Findings relating to pauci-immune disease (eg, anti-GBM disease, Wegener granulomatosis) and Goodpasture syndrome

  - Sinusitis, otitis, saddle nose deformity, hemoptysis

  - Lung consolidation, which suggests pulmonary hemorrhage

- Findings relating to IgA nephropathy (usually postinfectious) and other infectious glomerulonephritis

- Pharyngitis, gastroenteritis
- Impetigo, which is the most common cause of poststreptococcal glomerulonephritis worldwide

Causes:

- Immunoglobulin A (IgA) nephropathy and SLE are the most common causes. Other etiologies are less frequent but are more likely to lead to RPGN.
- Systemic diseases
  - Lupus nephritis class IV, IgA nephropathy
  - Goodpasture syndrome, Wegener granulomatosis, microscopic polyangiitis, Henoch-Schönlein purpura
  - Cryoglobulinemia, vasculitis
- Infectious causes
  - Poststreptococcal glomerulonephritis, which occurs 2-4 weeks after streptococcal sore throat or skin infection
  - Infective endocarditis, hepatitis B, hepatitis C
- Histologic transformation
  - In patients with class IV lupus nephritis, histologic transformation from one class to another is recorded in up to 40% of repeat biopsies.
  - The most likely transformation is from class II or III to class IV. Any other class may be superimposed on class V.

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Glomerulonephritis, Crescentic
Glomerulonephritis, Membranoproliferative
Glomerulonephritis, Membranous
Glomerulonephritis, Nonstreptococcal Associated With Infection
Glomerulonephritis, Poststreptococcal
Glomerulonephritis, Rapidly Progressive

Other Problems to be Considered:

Goodpasture syndrome is not the only cause of the pulmonary-renal syndrome (ie, renal failure, lung hemorrhage). Other important causes of pulmonary-renal symptoms include the following:

Severe cardiac failure complicated by pulmonary edema (often blood-tinged sputum) and prerenal azotemia

Renal failure from any cause complicated by hypervolemia and pulmonary edema

Immune complex–mediated vasculitides, including SLE, Henoch-Schönlein purpura, and cryoglobulinemia

Pauci-immune vasculitides, including Wegener granulomatosis and microscopic polyangiitis

Infections, such as Legionnaire disease

Renal vein thrombosis with pulmonary embolism

WORKUP

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Lab Studies:

- Urinalysis
  - No specific urinary finding can be used to accurately predict the presence of DPGN.
  - However, the finding of red blood cells and red blood cell casts strongly suggests glomerulonephritis. Proteinuria, wh

cells, and white blood cell casts may be present or absent. Renal biopsy should be obtained for histologic diagnosis a lupus, for classification.

- In patients with lupus who already have a histologic classification, an increase in urinary sediment abnormality should suspicion of histologic transformation. A repeat biopsy may be indicated if reclassification will guide management.

- A 24-hour urine collection is used for determination of protein and creatinine excretion. Creatinine in a 24-hour urine collec used to determine completeness of the collection as well as to calculate creatinine clearance. On average, in adults young years, creatinine excretion less than 15-20 mg/kg (lean body mass) for women or less than 20-25 mg/kg (lean body mass) suggests undercollection of the urine specimen. Values greater than these suggest overcollection. Both overcollection and undercollection lead to inaccurate estimation of creatinine clearance and, therefore, of glomerular filtration rate (GFR). A 2 urinary protein excretion in excess of 3.5 g is in the nephrotic range. A finding below 3.5 g indicates nonnephrotic proteinur specific pattern for DPGN is not identified, but nephrotic range proteinuria is more common.

- Complete blood count (CBC) findings
  - Anemia
  - Leukopenia, lymphopenia, and thrombocytopenia are often observed in SLE.

- Serum chemistry
  - Serum creatinine and urea nitrogen often are elevated.
  - Serum albumin may be low if the patient is nephrotic.

- Serologic tests
  - Positive antinuclear antibodies (ANAs) indicate lupus nephritis. Ninety-five percent of patients with SLE have positive however, it is not specific.
  - Positive tests for anti–double-stranded DNA (anti-dsDNA) and anti-Smith (anti-Sm) antibodies are more specific for lu (rising titers may indicate active or chronic disease).
  - Depressed complement levels of C3, C4, and CH50 may suggest SLE, infectious glomerulonephritis, poststreptococ

glomerulonephritis, or cryoglobulinemia.

- ANCAs are positive (>1:40) in almost all cases of Wegener granulomatosis. Eighty to 95% are cytoplasmic ANCA (C while 5-20% are perinuclear ANCA (P-ANCA). In one study, a positive result for C-ANCA was used to identify Weger granulomatosis, with a sensitivity and specificity of 65% and 88%, respectively, while a positive result for P-ANCA we identify Wegener granulomatosis with a sensitivity and specificity of 75% and 98%, respectively.

- Tests results that are positive for anti-GBM antibodies indicate consideration of anti-GMB disease (ie, idiopathic) and Goodpasture syndrome. Circulating anti-GBM antibodies are present in over 90% of patients, although the antibody t not correlate well with the manifestations or course of either the pulmonary or renal disease.

- A high titer of antistreptolysin O (ASO) shows recent streptococcal infection, indicating the possibility of poststreptoc glomerulonephritis. Healthy children of school age (eg, 6-12 y) commonly have titers of 200-300 Todd units per mL. A streptococcal pharyngitis, the antibody response peaks at about 4-5 weeks. Antibody titers decline rapidly in the next months and reach a slower decline after 6 months. Because 20% of patients with documented infection do not show the titer of antistreptolysin, other antistreptococcal antibodies such as anti-deoxyribonuclease (DNAse) B, anti-DNAs antihyaluronidase should be tested if ASO findings are negative.

- Throat culture findings for group A beta-hemolytic streptococci usually are negative at the time of glomerulonephritis, ASO titers peak.

- Serum IgA levels are elevated in as many as half of patients with IgA nephropathy.

Imaging Studies:

- Renal sonogram: This test is used to determine renal size, confirm the presence of 2 kidneys, and rule out structural lesion may be responsible for azotemia.

Procedures:

- Kidney biopsy

  - Indications, contraindications, and complications of percutaneous renal biopsy are discussed in the article Azotemia.

  - Renal biopsy is the criterion standard for diagnosis of anti-GBM nephritis. Obtain a renal biopsy for histologic diagnos lupus, for classification.

- In patients with lupus who already have a histologic classification, an increase in urinary sediment abnormality should suspicion of histologic transformation. A repeat biopsy may be indicated if reclassification will influence management

Histologic Findings:

Light microscopy

Light microscopy (see Image 1) shows a marked hypercellularity of endothelial (ie, endocapillary) and mesangial cells, capillary thickening (ie, wire loops) or obliteration, and inflammatory cell infiltration. In severe forms, epithelial cell proliferation with crescent formation, necrosis, and sclerosis may be present. Inflammatory infiltration and fibrosis also may present in the interstitium. End proliferation is typical of poststreptococcal glomerulonephritis.

Immunofluorescent microscopy

This technique shows (except for anti-GBM disease) a granular deposition of immunoglobulins, complement, and fibrin along the tubular basement membranes, and peritubular capillaries (see Image 2). Linear deposition occurs in the GBM in anti-GBM disea Image 2). Findings on immunofluorescence are negative in ANCA-associated glomerulonephritis. If radioimmunoassay is not av indirect immunofluorescence can be used to detect circulating anti-GBM antibodies in 60-80% of patients by incubating the patie serum with stored sections of healthy human kidneys

Electron microscopy

Using electron microscopy (see Image 3), electron dense deposits are visible in the mesangial, subendothelial, intramembranou subepithelial locations. In SLE, the mesangial and subendothelial deposits produce the typical wire loop lesions observed using microscopy. Tuboreticular inclusions may be observed within endothelial cells but are not pathognomonic. Tuboreticular inclusio may be observed in HIV nephropathy. In anti-GBM disease, the deposits are linear and intramembranous. In poststreptococcal glomerulonephritis, the deposits are subepithelial and appear as humps. Few or no deposits are visible in ANCA-associated glomerulonephritis.

Medical Care: Because of the high risk of ESRD, early aggressive therapy is indicated. Pulse methylprednisolone of 1 g daily fo followed by 1 mg/kg for 4-6 weeks and then tapered to 5-10 mg/d for maintenance therapy by 6 months, should be initiated as in therapy. Alternatively, prednisolone 1 mg/kg (not to exceed 80 mg/d) can be started and tapered as above. Additional induction

maintenance therapy may be indicated depending on the type of DPGN.

- Diffuse proliferative glomerulonephritis due to lupus
  - Pulse methylprednisolone, in combination with mycophenolate mofetil or cyclophosphamide, is indicated for DPGN d lupus nephritis. Studies show that mycophenolate mofetil is equal to or better than cyclophosphamide in inducing ren lupus nephritis and has fewer adverse effects. As a result, mycophenolate mofetil should be the drug of choice in cor with steroids.
  - In one study, 42 patients were randomized to receive prednisolone and mycophenolate for 12 months (21 patients, g prednisolone plus cyclophosphamide for 6 months followed by prednisolone and azathioprine for 6 months (21 patier 2). Of the 21 patients treated with mycophenolate mofetil and prednisolone (group 1), 81% had a complete remission had a partial remission, as compared with 76% and 14%, respectively, of the 21 patients treated with cyclophosphan prednisolone followed by azathioprine and prednisolone (group 2). Mycophenolate therapy was associated with fewe effects than cyclophosphamide.
  - In a more recent study, oral mycophenolate mofetil (initial dose, 1000 mg/d, increased to 3000 mg/d) was compared monthly intravenous cyclophosphamide (0.5 g per square meter of body-surface area, increased to 1 g per square m body-surface area) as induction therapy for active lupus nephritis over a 6-month period. The study protocol specifiec adjunctive care and the use and tapering of corticosteroids.
  - The study showed that complete remission was observed in 22.5% of patients who received mycophenolate mofetil a compared to 5.8% of patients treated with cyclophosphamide (p=0.005). There was no difference in the rate of partia remissions (29% vs 24%, respectively). There were fewer severe infections and hospitalizations, but patients receivir mycophenolate experienced more diarrhea. The investigators concluded that mycophenolate mofetil was more effect intravenous cyclophosphamide in inducing remission of lupus nephritis and had a more favorable safety profile.
  - Plasmapheresis, total lymphoid irradiation, and cyclosporine produce variable results but may be considered in sever refractory cases. Azathioprine is often used as an alternative to cyclophosphamide, particularly in patients concernec infertility.
- Diffuse proliferative glomerulonephritis due to immunoglobulin A nephropathy
  - Treatment is controversial, due in part to the indolent course of the disease. Patients with proteinuria less than 3 g/d, glomerular changes only, and preserved renal function (creatinine clearance >70 mL/min) may benefit from treatmen prednisone. Those with aggressive disease as manifested by hypertension, progressive azotemia, and nephrotic syn

may also be offered a trial of prednisone. Gross hematuria alone does not merit steroid use.

- In patients with progressive disease, fish oil should be considered. Most, but not all, studies thus far show benefit, alt doses.
- A tonsillectomy may reduce proteinuria and hematuria in those patients with recurrent tonsillitis.
- Corticosteroids in combination with cyclophosphamide may be tried in those who manifest crescentic DPGN on renal although no controlled trials exist. In one recent study, the use of mycophenolate mofetil did not retard disease progr
- No specific therapy is currently offered for milder forms of IgA nephropathy, although the use of ACE inhibitors and/o angiotensin receptor blockers is generally recommended.

- Anti-GBM antibody–induced diffuse proliferative glomerulonephritis/crescentic glomerulonephritis
  - Initiate treatment early.
  - Induction with steroids, as noted above, plus cyclophosphamide 0.5-1 mg per square meter of body-surface area intr for 3 months should be initiated, followed by maintenance therapy with azathioprine 1-1.5 mg/kg/d and tapering dose steroids.
  - Immunosuppression should be discontinued by 12 months, as there has been no benefit of additional therapy beyon period. Studies show that plasmapheresis is effective in anti-GBM disease. It is most effective if the patient is not yet dialysis. It should be provided over a course of 2 weeks.
- Pauci-immune diffuse proliferative glomerulonephritis/crescentic glomerulonephritis
  - Induction with steroids, as noted above, plus cyclophosphamide 0.5-1 mg per square meter of body-surface area intr for 3 months should be initiated, followed by maintenance therapy with azathioprine 1-1.5 mg/kg/d and tapering dose steroids.
  - Immunosuppression should be discontinued by 24 months, as there has been no benefit of additional therapy beyon period. Studies show that plasmapheresis is effective in DPGN due to pauci-immune glomerulonephritis even if the p on dialysis or has a serum creatinine level of greater than 5.6 mg/dL. It should be provided over a course of 2 weeks. who cannot tolerate or are not responsive to cyclosporine may benefit from mycophenolate mofetil, although large tri lacking.

- Diffuse proliferative glomerulonephritis due to infectious complications
  - The prognosis is good when crescent formation is absent.
  - Patients who are acutely uremic or show progression to end-stage renal failure need dialytic therapy or kidney transp
- Recurrences: Clinicians generally manage a recurrence in the native kidney or after transplantation similarly, adding appro supportive therapy for chronic renal failure.

Consultations:

- Involve a nephrologist in the initial management and as part of the multidisciplinary team.
- Involve a surgeon when progression to dialysis is inevitable for the creation of an arteriovenous fistula or a graft for dialysis insertion of a peritoneal dialysis catheter in the abdomen and for evaluation for kidney transplantation.
- Consult an otolaryngologist (ENT) and a pulmonologist for diagnosis and management of sinopulmonary disease in cases Wegener granulomatosis and Goodpasture syndrome, respectively.

Diet:

- Salt restriction (ie, <2 g/d) is recommended in all patients with hypertension and nephrosis.
- Protein restriction (ie, 40-60 g/d or 0.6-0.8 mg/kg/d) may slow progressive renal disease, but evidence in support of this vie being debated.
- In those with diuretic-resistant edema, fluid restriction may be required.

Activity: No restriction in activity is required, and patients should be encouraged to maintain physical activity as tolerated.

MEDICATION

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Corticosteroids and cytotoxic therapy can induce remission. Corticosteroids are potent anti-inflammatory agents and immunosuppressants. These drugs suppress both cellular and humoral response to tissue injury, thereby reducing inflammation prednisone generally is required for maintenance therapy. Cytotoxic drugs induce alkylation of DNA.

Drug Category: *Corticosteroids* -- Have both anti-inflammatory (glucocorticoid) and salt-retaining (mineralocorticoid) properti Glucocorticoids have profound and varied metabolic effects. In addition, these agents modify the body's immune response to div stimuli.

	Prednisone (Deltasone, Orasone, Meticorten, Sterapred) -- Most

Drug Name	patients require long-term oral prednisone after inducing remission. Immunosuppressants for treatment of autoimmune disorders may decrease inflammation by reversing increased capillary permeability and suppressing PMN activity.
Adult Dose	5-60 mg/d PO qd or divided bid/qid
Pediatric Dose	4-5 mg/m^2/d PO; alternatively, 0.05-2 mg/kg PO divided bid/qid
Contraindications	Documented hypersensitivity; viral infection; peptic ulcer disease; hepatic dysfunction; connective tissue infection; fungal or tubercular skin infection; GI disease
Interactions	Coadministration with estrogens may decrease prednisone clearance; concurrent use with digoxin may cause digitalis toxicity secondary to hypokalemia; phenobarbital, phenytoin, and rifampin may increase metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections may occur with glucocorticoid use
Drug Name	Methylprednisolone (Solu-Medrol) -- For pulse therapy. Decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability.
Adult Dose	15-30 mg/kg/d IV over 1 h for 3 d, typically 1 g/d IV for 3 d
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; viral, fungal, or tubercular skin infection
Interactions	Coadministration with digoxin may increase digitalis toxicity secondary to hypokalemia; estrogens may increase levels of methylprednisolone; phenobarbital, phenytoin, and rifampin may decrease levels of methylprednisolone (adjust dose); monitor patients for hypokalemia when taking medication concurrently with diuretics
Pregnancy	C - Safety for use during pregnancy has not been established.

Precautions	Hyperglycemia, edema, osteonecrosis, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, growth suppression, myopathy, and infections are possible complications of glucocorticoid use

Drug Category: *Cytotoxins* -- Inhibit cell growth and proliferation.

Drug Name	Cyclophosphamide (Cytoxan) -- DOC in DPGN. Chemically related to nitrogen mustards. As an alkylating agent, the mechanism of action of the active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells. Low dose is used when creatinine clearance is <33 mL/min. Maintain white blood cell count >2000/mL. A dose of 50-100 mg/m^2 PO qd is associated with a higher incidence of hemorrhagic cystitis.
Adult Dose	0.5-1 g/m^2 IV bolus over 60 min, then every mo for 5 doses, then q3mo until 1-2 y after remission; not to exceed 4 y of cytotoxic therapy
Pediatric Dose	0.5-1 g/m^2 IV bolus over 60 min, then every mo for 5 doses, then q3mo until 1-2 y after remission; not to exceed 4 y of cytotoxic therapy
Contraindications	Documented hypersensitivity; severely depressed bone marrow function
Interactions	Allopurinol may increase risk of bleeding or infection and enhance myelosuppressive effects of cyclophosphamide; may potentiate doxorubicin-induced cardiotoxicity; may reduce digoxin serum levels and antimicrobial effects of quinolones; chloramphenicol may increase the half-life of cyclophosphamide while decreasing metabolite concentrations; may increase effect of anticoagulants; coadministration with high doses of phenobarbital may increase the rate of metabolism and leukopenic activity of cyclophosphamide; thiazide diuretics may prolong cyclophosphamide-induced leukopenia and neuromuscular blockade by inhibiting cholinesterase activity
Pregnancy	D - Unsafe in pregnancy
Precautions	Regularly examine hematologic profile (particularly neutrophils and platelets) to monitor for hematopoietic suppression; regularly examine

	urine for RBCs, which may precede hemorrhagic cystitis
Drug Name	Mycophenolate (CellCept, Myfortic) -- Inhibits inosine monophosphate dehydrogenase (IMPDH) and suppresses denovo purine synthesis by lymphocytes, thereby inhibiting their proliferation. Inhibits antibody production. Two formulations are available and are not interchangeable. The original formulation, mycophenolate mofetil (MMF, Cellcept) is a prodrug that once hydrolyzed in vivo, releases the active moiety mycophenolic acid. A newer formulation, mycophenolic acid (MPA, Myfortic) is an enteric-coated product that delivers the active moiety.
Adult Dose	0.5-1 g PO bid
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity
Interactions	In combination with either acyclovir or ganciclovir may result in higher levels for both interacting drugs due to competition for renal tubular excretion; aluminum/magnesium present in some antacids, and cholestyramine containing products may decrease absorption, reducing levels (do not administer together); probenecid may increase levels of mycophenolate; salicylates and azathioprine may increase toxicity; may decrease levonorgestrel AUC; may decrease live virus vaccine immune response; when administered in combination with theophylline may increase free fraction levels of theophylline
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Increases risk for infection (monitor blood count); severe renal impairment (CrCl <25 mL/min) may have increased adverse effects due to increased free MPA; caution in active peptic ulcer disease; incidence of malignancies and lymphoma consistent with that reported for other immunosuppressants (0.9%); commonly causes constipation, nausea, diarrhea, urinary tract infection, and nasopharyngitis; rare reports include interstitial lung disorders, colitis, pancreatitis, intestinal perforation, GI hemorrhage, gastric ulcers, duodenal ulcers, and ileus; do not chew, crush, or cut Myfortic tab

FOLLOW-UP

Further Inpatient Care:

- Patients should be monitored closely for steroid-induced diabetes, electrolyte abnormalities, abnormal gas exchange, and opportunistic infections.

Further Outpatient Care:

- Renal function should be monitored closely.
- Hypertension should be treated aggressively.
- Patients should be monitored closely for steroid-induced diabetes and opportunistic infections.

Deterrence/Prevention:

- No clear risk factors are associated with development of DPGN; thus, no known preventive methods can be advocated.

Complications:

- End-stage renal disease
- Complications of steroid or cytotoxic therapy are discussed under Medication. The commonly encountered complications i diabetes, opportunistic infections, and infertility.
- Complications of the specific diseases are discussed in other articles.

Prognosis:

- Evidence of glomerulosclerosis, fibrous crescents, tubular atrophy, and, particularly, interstitial fibrosis using light microsco indicates advanced disease and a poor prognosis.

- Being a male is a higher risk factor for a bad prognosis. Other risk factors associated with a bad prognosis include heavy p hypertension, interstitial fibrosis, oliguria, and azotemia at presentation.
- Renal survival is best with IgA and worse with anti-GBM disease. In some series, the rate of progression to ESRD in class was 50% during a 2-year follow-up.
- Overall, about 50% of patients with DPGN require dialysis within 6-12 months after presentation.

Patient Education:

- Educate patients on the disease process, renal prognosis, complications of therapy, and importance of adhering to the trea plan. The importance of keeping appointments must be emphasized.
- For those with advanced renal failure, options for renal replacement therapy (Ie, hemodialysis, peritoneal dialysis, transplai should be fully discussed.
- For excellent patient education resources, visit eMedicine's Kidneys and Urinary System Center. Also, see eMedicine's pat education article Blood in the Urine.
- For further information, see Mayo Clinic - Kidney Transplant Information.

MISCELLANEOUS

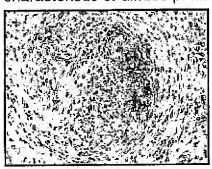
Medical/Legal Pitfalls:

- Delay in diagnosis and treatment may result in rapid progression to ESRD.
- Inadequate monitoring of cytotoxic therapy may result in life threatening complications.

Special Concerns:

- Infertility may result from use of cyclophosphamide; thus, informed consent should be obtained before instituting this form

Caption: Picture 1. Diffuse proliferative glomerulonephritis (DPGN). Light microscopy (trichrome stain) shows globally increased cellularity, numerous polymorphonuclear cells, cellular crescent (at left of photomicrograph) and fibrinoid necrosis (brick red staining at right of photomicrograph). These findings are characteristic of diffuse proliferative glomerulonephritis.



View Full Size Image

eMedicine Zoom View (Interactive!)

Picture Type: Photo

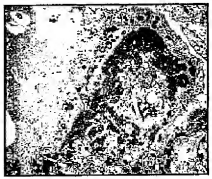
Caption: Picture 2. Diffuse proliferative glomerulonephritis (DPGN). Immunofluorescent microscopy shows (except for anti–glomerular basement membrane [GBM] disease) a granular deposition of immunoglobulins, complement, and fibrin along the GBM, tubular basement membranes, and peritubular capillaries (image 2a). Linear deposition occurs in the GBM in anti-GBM disease (image 2b).

View Full Size Image

eMedicine Zoom View (Interactive!)

Picture Type: Photo

Caption: Picture 3. Diffuse proliferative glomerulonephritis (DPGN). Using electron microscopy, electron dense deposits are visible in the mesangial, subendothelial, intramembranous, and subepithelial locations.



View Full Size Image

eMedicine Zoom View (Interactive!)

Picture Type: Photo

BIBLIOGRAPHY

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